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Autologous

Molecular Monitoring after Autologous Stem Cell Transplantation and Preemptive Rituximab Treatment of Molecular Relapse; Results from the Nordic Mantle Cell Lymphoma Studies (MCL2 and MCL3) with Median Follow-Up of 8.5 Years

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A B S T R A C T

The main objectives of the present study were to monitor minimal residual disease (MRD) in the bone marrow of patients with mantle cell lymphoma (MCL) to predict clinical relapse and guide preemptive treatment with rituximab. Among the patients enrolled in 2 prospective trials by the Nordic Lymphoma Group, 183 who had completed autologous stem cell transplantation (ASCT) and in whom an MRD marker had been obtained were included in our analysis. Fresh samples of bone marrow were analyzed for MRD by a combined standard nested and quantitative real-time PCR assay for Bcl-1/immunoglobulin heavy chain gene (*IgH*) and clonal *IgH* rearrangements. Significantly shorter progression-free survival (PFS) and overall survival (OS) was demonstrated for patients who were MRD positive pre-ASCT (54 patients) or in the first analysis post-ASCT (23 patients). The median PFS was only 20 months in those who were MRD-positive in the first sample post-ASCT, compared with 142 months in the MRD-negative group ($P < .0001$). OS was 75% at 10 years and median not reached in the MRD-negative group, compared with only 35 months in the MRD-positive group ($P < .0001$). Of the 86 patients (47%) who remained in continuous molecular remission, 73% were still in clinical remission after

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10 years. For all patients, the median time from ASCT to first molecular relapse was 55 months, with a continuous occurrence of late molecular relapses. Fifty-eight patients who experienced MRD relapse received rituximab as preemptive treatment on 1 or more occasions, and in this group, the median time from first molecular relapse to clinical relapse was 55 months. In most cases, rituximab converted patients to MRD negativity (87%), but many patients became MRD-positive again later during follow-up (69%). By multivariate analysis, high-risk Mantle Cell Lymphoma International Prognostic Index score and positive MRD status pre-ASCT predicted early molecular relapse. In conclusion, preemptive rituximab treatment converts patients to MRD negativity and likely postpones clinical relapse. Molecular monitoring offers an opportunity to select some patients for therapeutic intervention and to avoid unnecessary treatment in others. MRD-positive patients in the first analysis post-ASCT have a dismal prognosis and thus are in need of novel strategies.

INTRODUCTION

High-dose therapy with autologous stem cell transplantation (ASCT) as consolidation after first-line immunochemotherapy is considered by many to be the preferred first-line treatment for the majority of younger patients with mantle cell lymphoma (MCL) [1]. This strategy has led to greatly improved outcomes for patients with MCL over the last 10 to 15 years [2-5]. Not all patients may benefit from such an aggressive approach, however. It is well known that a more indolent subtype of MCL with nonnodal, leukemic disease and absence of SOX11 has a more favorable prognosis [6]. Low-risk MCL, as measured by the Mantle Cell Lymphoma International Prognostic Index (MIPI), and low Ki-67 proliferative index have better outcome, whereas high MIPI score, elevated Ki-67 proliferative index, and/or blastoid morphology indicate more aggressive disease, early relapse, and inferior survival [7,8].

Monitoring of minimal residual disease (MRD) has proven to be of relevance in patients with MCL to evaluate the quality of remission and predict clinical relapse [4,9-11]. Thus, the Nordic MCL2 and MCL3 trials included efforts to reverse molecular relapse and delay clinical relapse by administering rituximab as a so-called preemptive strategy [4,11,12], as opposed to rituximab maintenance therapy, a strategy that was later found to prolong progression-free survival (PFS) in elderly patients after conventional immunochemotherapy [13], as well as after ASCT in younger patients [14]. Here we report the long-term results from systematic MRD monitoring and preemptive rituximab treatment in the Nordic MCL2 and MCL3 studies.

PATIENTS AND METHODS

Study Population and Treatment

A total of 183 patients included in the Nordic MCL2 and MCL3 trials who had completed ASCT and in whom a PCR marker for MRD had been obtained were included in our present analysis [4,11]. Both protocols were approved by Medical Agencies and Ethics Committees, and informed consent was obtained for each patient. All diagnoses of MCL had been confirmed by central pathology review. Staging included computed tomography (CT) scans and bone marrow (BM) aspiration and biopsy. Clinical and molecular response evaluation was performed pre-ASCT and at 2 to 3 months, at 6 months, and then every 6 months post-ASCT, until relapse or completion of 5 years of follow-up. Details on the Nordic MCL treatment regimens have been outlined previously [4,11]. In brief, in the Nordic MCL2 trial, patients received a total of 6 cycles of alternating maxi-CHOP-R (cyclophosphamide, doxorubicine, vincristine, rituximab, prednisolone, and R-Ara-C [cytarabine, rituximab]), followed by ASCT. In the Nordic MCL3 trial, the induction regimen remained unchanged, but responding patients not in complete remission before ASCT received yttium-90 ibritumomab tiuxetan. Treatment outcome with regard to overall survival (OS), event-free survival (EFS), and PFS, as well as adverse events, were similar in the MCL2 and MCL3 trials [11]. Patients who developed a solely molecular relapse during follow-up in both studies received 4 weekly doses of rituximab (375 mg/m^2). This treatment could be repeated in case of recurrent molecular relapses.

PCR Analysis for MRD

Fresh samples of peripheral blood (PB) and BM were analyzed at the central laboratory in Copenhagen. DNA was extracted with the QIAprep Miniprep Kit (Qiagen, Valencia, CA) and used for PCR primer design. The DNA content was determined by spectrophotometry. A combined standard nested and quantitative real-time PCR assay for Bcl-1/immunoglobulin heavy chain gene (*IgH*) and clonal *IgH* rearrangements was used to estimate MRD involvement in consecutive post-ASCT BM/PB samples as described in detail in previous reports [4,12]. BM samples were more sensitive for detection of MRD; thus, in the present analysis, we used MRD data only from BM.

Eligibility for Preemptive Treatment

The definition of molecular relapse after ASCT was based on 2 sets of criteria. When the first post-transplantation BM sample was standard nested PCR-negative, a conversion to standard nested PCR-positive in any subsequent BM sample was defined as a molecular relapse. When the first post-transplantation BM sample was standard nested PCR-positive, we awaited the subsequent BM sample. If this sample was also standard nested PCR-positive, then we proceeded to real-time quantitative PCR analysis of these 2 consecutive samples. A significant (>5-fold) increase in the real-time quantitative PCR detectable MRD level was defined as a molecular relapse. PCR-positive follow-up samples were sequenced to secure identity with the original IGHV/t(11;14) sequence. Preemptive treatment with 4 weekly doses of rituximab should be followed by a subsequent MRD analysis. The median time from preemptive therapy until the next MRD testing was 2 months.

Endpoints and Statistics

PFS was calculated from the date of ASCT or date of molecular relapse until the date of clinical relapse or progression, death from lymphoma, or date of last clinical follow-up. Time to molecular progression was calculated from date of ASCT until first molecular relapse or the date of the last MRD-negative molecular follow-up. OS was defined as the time from ASCT to death from any cause or the last date of follow-up. Survival analysis was performed according to the Kaplan-Meier method [15], and differences between subgroups were analyzed using the log-rank test. The association between prognostic factors and outcomes was evaluated using a Cox proportional hazards model. The MIPI and MIPI-combined (MIPI-C) were calculated according to the approach of Hoster et al. [7,16,17].

RESULTS

Outcomes Relative to MRD Status Pre- and Post-ASCT

An MRD marker for Bcl-1 or IgH rearrangement was obtained in 215 patients, including 94 of the 160 patients (59%) in the MCL2 trial and 121 of the 160 patients (76%) in the subsequent MCL3 trial. Of these, 183 patients who completed ASCT were included in our present analysis, with a median follow-up of 8.5 years among survivors. A flow chart showing outcomes for all patients in this study is presented in Figure 1. Patients' characteristics are shown in Table 1. PFS and OS for the 183 patients recruited were not significantly different from those of the 97 patients who also completed ASCT and in whom no MRD marker was obtained (data not shown). Pre-ASCT, 54 patients (42%) were MRD-positive. Both PFS and OS were significantly shorter in these patients than in the MRD-negative patients, for whom median PFS had not been reached (Figure 2A, B). In the first sample post-ASCT, only 23 (13%) of were still MRD-positive. The median PFS was only 20 months in this group, compared with 142 months in the MRD-negative group (Figure 2C). This translated into a significantly longer OS in the MRD-negative patients of 75%

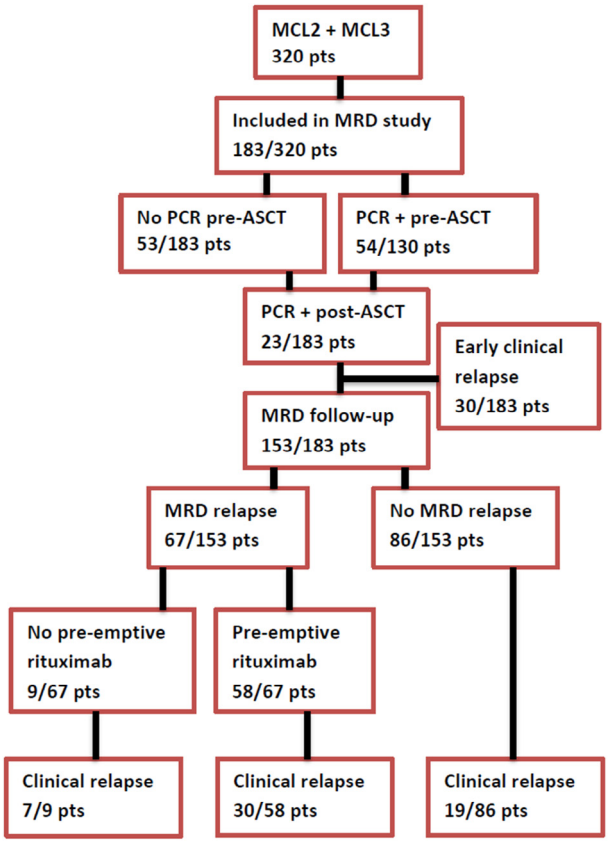

Figure 1. Flow chart with outcomes for all 183 patients in the MRD study.

at 10 years and median not reached, compared with a median OS of only 35 months in the MRD-positive group ($P < .0001$) (Figure 2D).

Risk of Clinical Relapse after Molecular Relapse

For all 183 patients, the median time from ASCT to first molecular relapse was 55 months (Figure 3). Sixty-seven patients were eligible for preemptive rituximab, and 58 received this therapy as planned. The median time from first molecular relapse until clinical relapse for this group was 55 months (Figure 4A). Eighty-six of the 183 patients (47%) remained MRD-negative in all analyses performed after ASCT. Of these, 63 (73%) are still alive and in clinical remission after a median follow-up of 8.5 years (Figure 4B), whereas 19 (22%) relapsed clinically and 4 died from other causes. In contrast, of the 97 patients (53%) who were MRD-positive at any time post-ASCT, 64 (66%) also relapsed clinically. In 27 patients, this occurred simultaneously or within 3 months after the molecular relapse, and the majority did not receive preemptive rituximab. Importantly, there were no signs of plateaus on the curves for time to molecular progression in this cohort of younger MCL patients treated up front with intensive immunochemotherapy followed by ASCT and subsequent preemptive rituximab. No serious adverse events were reported for the patients treated with rituximab based on this MRD-guided approach.

Table 1
Characteristics of the 183 Patients Followed for MRD

Variable	Category	Value
Male sex, n (%)		140 (77)
Age, yr, median (range)		57 (28-65)
Stage IV, n (%)		170 (93)
MIPI score (n = 182), n (%)	Low	83 (46)
	Intermediate	59 (32)
	High	40 (22)
MIPI C score (n = 156), n (%)	Low	58 (37)
	Low/intermediate	44 (28)
	High/intermediate	33 (21)
	High	21 (13)
Cytology (n = 182), n (%)	Common	151 (83)
	Blastoid	31 (17)
% Ki-67 (n = 157), n (%)	0-29	98 (63)
	≥30	59 (38)

MRD indicates minimal residual disease; MIPI, Mantle Cell Lymphoma International Prognostic Index.

Outcomes after Preemptive Rituximab Treatment

The outcomes after preemptive rituximab therapy for 28 patients in continuous remission (48%) and 30 patients who experienced clinical relapse (52%) are shown in Figure 5A, B. Twenty-five patients (43%) received rituximab for molecular relapse on multiple occasions. Out of a total of 92 rituximab treatments in which subsequent samples for MRD were obtained, 80 (87%) of led to MRD negativity. Among all of the rituximab-treated patients who converted to MRD negativity, 34 (69%) became MRD-positive again in a subsequent sample, suggesting that rituximab had only a temporary effect. Typically, patients who experienced a clinical relapse had a shorter duration of molecular remission after preemptive treatment (Figure 5B) compared with those who remained in clinical remission during follow-up (Figure 5A). Moreover, molecular relapse often coincided with clinical relapse in this group.

Predictors for Molecular Relapse

We further investigated whether the MIPI and MIPI-C, known clinical prognosticators, could predict molecular relapse in our patient cohort (Figure 6). Patients categorized as high risk by the MIPI and MIPI-C had significantly shorter time to molecular progression (25 months and 19 months) compared with the lower-risk groups (Figure 6A, B; $P < .0001$). On multivariate analysis (Table 2), significant predictors for molecular relapse were MIPI high risk at diagnosis (hazard ratio, 1.908; 95% confidence interval, 1.368 to 2.661; $P = .0001$) and detection of MRD before ASCT (hazard ratio, 2.465; 95% confidence interval, 1.486 to 4.090; $P = .0005$). Nevertheless, even patients at low risk and those who were MRD-negative pre-ASCT continued to become MRD-positive during follow-up.

DISCUSSION

In the present study, we aimed to investigate in detail the kinetics and consequences of molecular relapses after ASCT with long-term follow-up in MCL. In line with previous reports [9,18], we demonstrated that molecular monitoring is feasible and provides valuable information on the quality of remission and risk of clinical relapse. The subgroup of patients who were MRD-positive in the first sample post-ASCT had particularly poor outcomes. Systematic preemptive treatment of molecular relapses with single-agent rituximab therapy converted most patients to MRD negativity, and this procedure could be repeated successfully. Most likely this postponed clinical relapse; however, given that those results were uncontrolled, the clinical benefit can be assessed only indirectly.

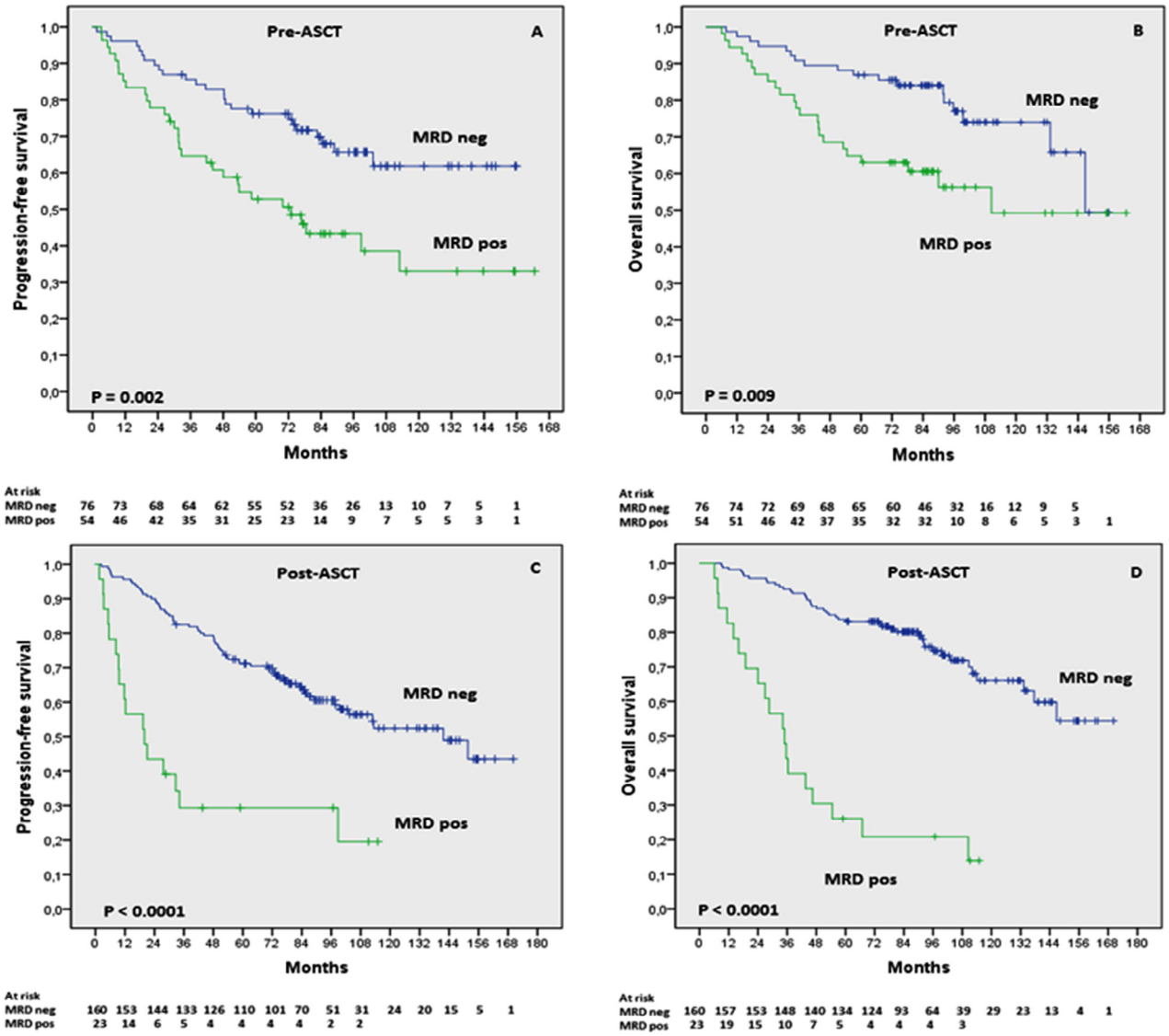

Figure 2. PFS and OS relative to MRD status before and after ASCT.

As data from long-term follow-up of patients receiving modern intensive immunochemotherapy and ASCT continue to emerge, a consistent picture of late recurrence has been well documented by us and others [19-21]. In parallel, we observed a continuous pattern of MRD relapses that did not subside even after 5 to 10 years and included all risk groups. Therefore, with present therapies, MCL remains incurable, and novel approaches are needed [22]. Prognostic models for MCL, the clinical MIPI [7], and the biological MIPI-B [17] that include the proliferation marker Ki-67 assign patients to high-, intermediate-, and low-risk groups. Recently, a modified combination of Ki-67 and MIPI (MIPI-C) was shown to be superior to MIPI and MIPI-B for risk stratification in cohorts from the European MCL Younger and MCL Elderly trials [16]. We observed that high-risk patients so categorized based on the MIPI and MIPI-C had a significantly shorter time from ASCT to molecular relapse; however, there was no clear separation between curves for other risk groups with respect to time to molecular progression.

In previous studies, we and other demonstrated the ability of rituximab to induce effective clearance of MRD in MCL [12,23,24]. The present series is the largest prospective study to investigate the preemptive strategy with prolonged molecular and clinical follow-up in patients with MCL. The median time from molecular relapse until clinical relapse in 58 patients who received rituximab was as long as 55 months, and a subgroup (48%) was still in clinical remission at the end of follow-up. Despite the clear evidence that the preemptive strategy can repeatedly reduce the tumor load in the bone marrow to below the detection limit of sensitive PCR, and the prolonged time to clinical relapse in treated patients, the data do not strictly document a clinical benefit of the preemptive strategy. Only a randomized trial can resolve this issue.

The high rate of MRD recurrence observed after rituximab therapy in our trial, and thus the need to repeat the preemptive strategy, supports a more continuous approach like maintenance rituximab administered every 2 to 3 months,

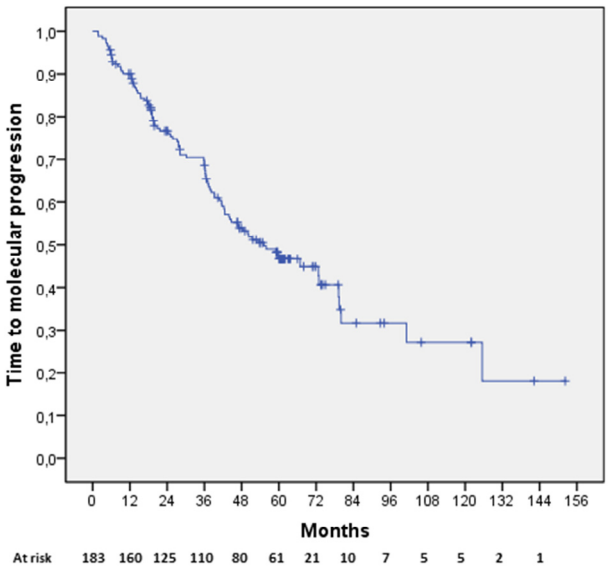

Figure 3. Proportion of patients free of molecular progression after ASCT.

which has been tested in 2 randomized trials. The European Mantle Cell Lymphoma Network Elderly trial showed significant improvements in both PFS and OS following R-CHOP [13], and the LyMa Study in younger patients following ASCT showed improved EFS and PFS in the maintenance arm [14]. MRD-guided maintenance initiated only after molecular relapse rather than in all patients may be an option. Alternatively, other treatments like lenalidomide, bortezomib, or novel targeted therapies (eg, ibrutinib, venetoclax) may be more effective in maintaining stable molecular remission and thereby preventing clinical relapse.

In line with a previous report [25], another category of patients at elevated risk for MRD relapse and clinical relapse in our trial was the pre-ASCT MRD-positive group. These patients also could potentially benefit from maintenance rituximab therapy. Another possible strategy for this group would be to provide additional treatment before ASCT to achieve MRD-negative status before continuing to transplantation or to consider allogeneic stem cell transplantation instead of ASCT. The question of whether patients who are MRD-negative before ASCT really require ASCT is also relevant. A significant proportion of patients (47%) remained MRD-negative in all analyses during long-term follow-up, and the PFS for this group was very favorable. Observation without further intervention might be a reasonable strategy for this subgroup. Thirteen percent of patients were not in molecular remission at the first analysis post-ASCT, and for this group the prognosis was dismal, with a high rate of early recurrence and short survival. It is unlikely that single-agent rituximab would significantly improve outcomes in these very aggressive cases, and other treatments should be considered, such as allogeneic stem cell transplantation in younger fit patients or novel targeted therapies.

Technically, to extend the application of MRD monitoring, a mandatory lymph node biopsy or extended Bcl-1 and IgH primer design would be important to increase the proportion of patients with a molecular marker [26]. Furthermore, novel approaches like next-generation sequencing (NGS) and droplet digital PCR (ddPCR) are currently being explored as an alternative to quantitative PCR in patients with hematologic malignancies [27-29]. Even though results in MCL have been encouraging so far, NGS has the disadvantage of high costs and this methodology is not broadly available at present. This might be changing with the increases in commercially available sequencing. The ddPCR method is less labor-intensive than quantitative PCR in bypassing the use of dilution-based standard curves, and results in MCL are promising with sensitivity and reproducibility at least comparable to those of quantitative PCR [29]. However, until further studies confirm these findings, quantitative PCR remains the standard technique for MRD monitoring in MCL. Importantly, adherence to the Euro-MRD guidelines [30] for MRD analysis ensures reliability and standardization across laboratories.

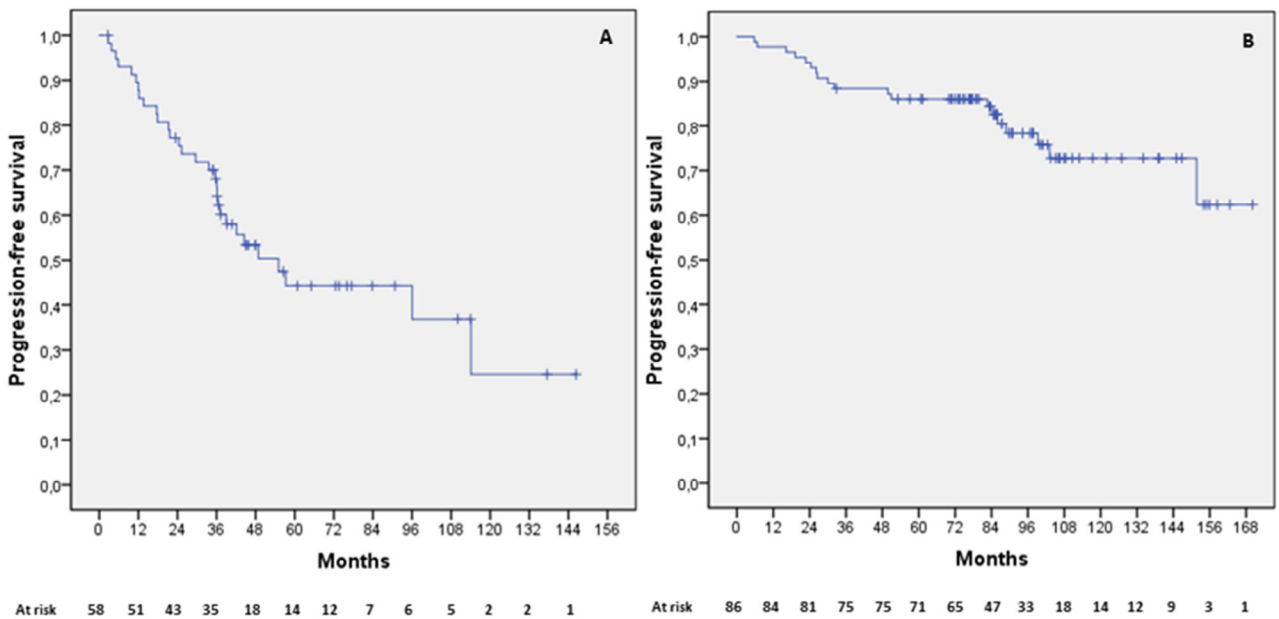

Figure 4. PFS in patients with molecular relapse (A) or in continuous molecular remission (B) after ASCT.

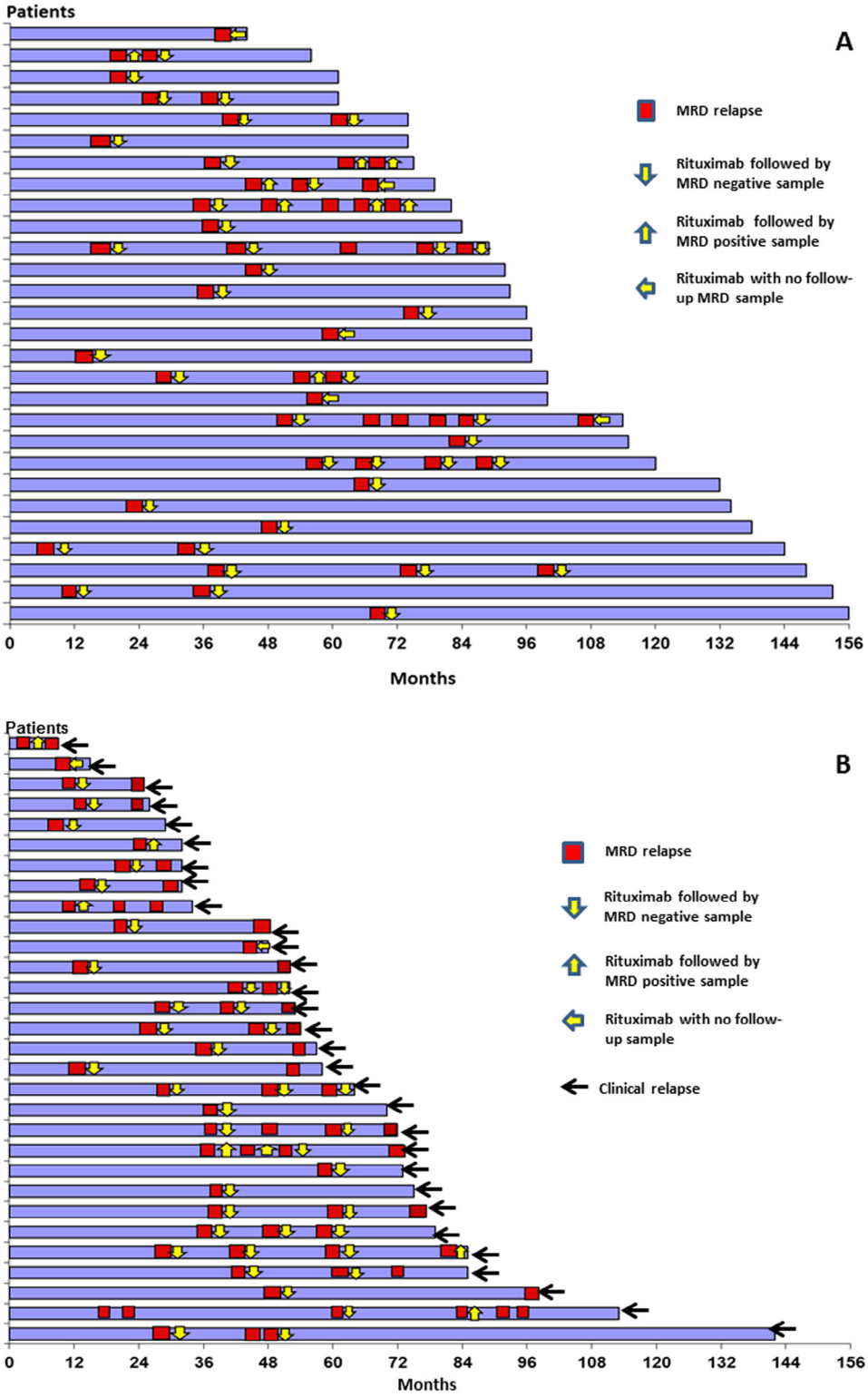

Figure 5. Patients treated with preemptive rituximab for solely molecular relapse.

In conclusion, in this large prospective study, we confirm the importance of inducing a molecular remission in MCL. The continuous pattern of molecular relapse in all risk groups supports the current view that MCL is incurable. Likewise, preemptive rituximab treatment of MRD relapse reinduced molecular remission, but in many cases this remission was not durable. Therefore, maintenance rituximab may be a preferred strategy to keep patients in stable molecular

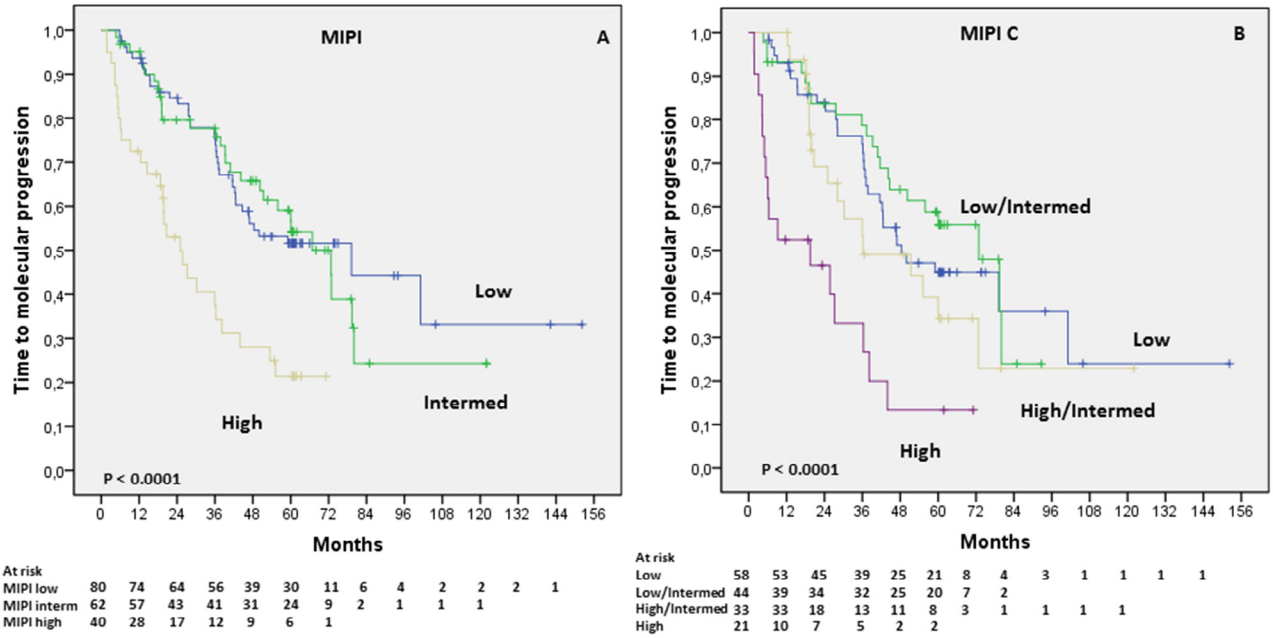

Figure 6. Time to molecular progression from ASCT relative to MIPI prognosticators.

Table 2
Multivariate Analysis for Prediction of Time to Molecular Progression from ASCT in 115 Patients with Available Data on MIPI, Pre-ASCT MRD, Cytologic Variant, and Ki-67 Proliferative Index

Parameter	Time to Molecular Progression (n = 115)		
	P Value	HR	95% CI
MIPI high versus intermediate/low	.0001	1.908	1.368-2.661
MRD-positive versus -negative pre-ASCT	.0005	2.465	1.486-4.090
Male versus female	.8377	1.086	0.494-2.386
Age ≥60 versus <60 yr	.7260	1.109	0.621-1.981
Common versus blastoid	.5143	.784	0.377-1.631
%Ki-67 ≥30 versus <30	.3126	1.308	0.777-2.204

MIPI indicates Mantle Cell Lymphoma International Prognostic Index; ASCT, autologous stem cell transplantation; MRD, minimal residual disease; HR, hazard ratio; CI, confidence interval.

remission and delay clinical relapse. MRD monitoring has the potential to become a useful tool for identifying patients who should receive interventions aimed to prolong clinical remission and to spare a significant proportion of patients from unnecessary treatment. Of particular concern is the poor prognosis of those who are MRD-positive in the first analysis post-ASCT. For this group, novel strategies are urgently needed.

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Authorship statement: All authors participated in the creation of protocols during Nordic Lymphoma Group meetings and contributed to data collection and reporting. A.K., L.B.P., C.W.E., S.H., P.B. and C.H.G. analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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